DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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Ms. Kathleen M. Sanzo, Esq.
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1111 Pennsylvania Avenue, NW
Washington, DC 20004

Re: Docket No. FDA-2005-P-0259 (formerly Docket No. 2005P-0305)

Dear Ms. Sanzo:

This letter responds to the citizen petition dated July 29, 2005, that you submitted on behalf of your client Biostratum, Inc. (Biostratum), asking the Food and Drug Administration (FDA) to determine the regulatory status of pyridoxamine for use in dietary supplements.

In accordance with Title 21 of the Code of Federal Regulations (CFR), section 10.30(e)(3) (21 CFR 10.30(e)(3)), and for the reasons stated below, this letter is to advise you that FDA is granting your petition in part and denying your petition in part.

I. Procedural History

On July 29, 2005, you submitted the above-referenced citizen petition requesting that FDA (1) state in writing that dietary supplements that contain pyridoxamine are adulterated under the Federal Food, Drug, and Cosmetic Act (the Act); (2) exercise its enforcement authority under the Act to remove dietary supplements containing pyridoxamine from interstate commerce in the United States; and (3) not place the citizen petition in the agency's docket for premarket notifications for new dietary ingredients (Docket No. 2004N-0454) because the petition is focused on legal, scientific, and public health issues presented by dietary supplements that contain pyridoxamine.

Your petition states that BioStratum is the manufacturer of Pyridorin (pyridoxamine dihydrochloride) and that Pyridorin is the subject of an investigational new drug application (IND) that was filed with FDA in July 1999. According to FDA's records, the IND was received on August 2, 1999, and became effective on September 1, 1999 (Ref. 1). Your petition further states that substantial clinical investigations have been instituted to study the use of this drug to slow or prevent the progression of diabetic nephropathy (kidney disease), and that the existence of those studies has been made public.

In response to your petition, FDA published a notice in the Federal Register on November 18, 2005 (70 Fed. Reg. 69,976) in which we set forth our tentative conclusions on the regulatory status of pyridoxamine and solicited public comment. In the notice, FDA tentatively

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concluded that "pyridoxamine, the active moiety[1] of pyridoxamine dihydrochloride, is excluded from the dietary supplement definition under the exclusion clause in 21 U.S.C. 321(ff)(3)(B)(ii) and therefore may not be marketed as or in a dietary supplement." In accordance with 21 CFR 10.30(h)(3), we asked for comments in response to your citizen petition and, in particular, for "information, if any, that would bear on pyridoxamine's prior marketing as a dietary ingredient or as a food, as well as any other information that would inform the agency's final decision on the status of pyridoxamine."

FDA received 11 comments in response to our November 18, 2005 notice. Five comments were received from the dietary supplement industry. Two of these were from dietary supplement manufacturers and three from a dietary supplement trade association. These comments generally favored the continued availability of pyridoxamine as a dietary supplement and disagreed with FDA's tentative conclusion in the November 18, 2005 Federal Register notice. One included a request for an extension of the comment period, which FDA did not grant. Four comments were received from the original petitioner. These comments generally offered information and views to rebut the comments from the dietary supplement industry. One comment was received from a practicing physician who urged FDA to remove pyridoxamine supplements from the marketplace, stressing the urgent need for improved therapies for diabetic kidney disease and the importance of preserving incentives for continued research on the efficacy of pyridoxamine for this use. One comment was received from a consumer, who similarly stressed the potential value of pyridoxamine in preventing kidney disease and other complications of diabetes; however, this comment did not address any of the issues raised in the petition or in FDA's Federal Register notice. Several of the comments provided information bearing on the date of pyridoxamine's first marketing as a dietary supplement or as a food, or information otherwise relevant to the agency's final decision on the status of pyridoxamine. We address the information provided in these comments below.

II. FDA's Response to the Citizen Petition

A. Summary of Decision

For the reasons given below, FDA is granting your citizen petition in part and denying your citizen petition in part.

FDA is granting your request not to file your citizen petition in the docket for new dietary ingredient notifications (Docket No. 2004N-0454). Instead, FDA has established a separate docket for your citizen petition (Docket No. 2005P-0305).

FDA is denying the part of your petition concerning enforcement action against pyridoxamine-containing products sold as dietary supplements because a request for enforcement action cannot be the subject of a citizen petition. A citizen petition provides a mechanism for interested persons to request that FDA issue, amend, or revoke a regulation or order, or that the

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[1] Under 21 CFR 316.3(b)(2), "active moiety" means "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance."

agency take or refrain from taking any other form of *administrative action* (emphasis added) (21 CFR 10.25(a)). A citizen petition cannot be used to request enforcement action because "administrative action," as defined in 21 CFR 10.3(a), does not include the referral of apparent violations of law to U.S. attorneys for the institution of civil or criminal proceedings or an act in preparation of such a referral. Thus, your request for enforcement action is a request that is not within the scope of a citizen petition, and we are denying this part of your petition. This denial does not affect FDA's enforcement authority under the Act, however. Under its authority to refer civil or criminal violations of the Act to the Department of Justice, the agency may take action against pyridoxamine products that violate the Act, as with any other product under its jurisdiction.

FDA is also denying your request that the agency state in writing that dietary supplements that contain pyridoxamine are adulterated under the Act because our conclusion on the regulatory status of pyridoxamine makes it unnecessary to reach this question. In your petition, you stated that products containing pyridoxamine are adulterated under 21 U.S.C. 342(f) because (1) pyridoxamine is not a grandfathered dietary ingredient; (2) pyridoxamine has never been the subject of a 75-day new dietary ingredient notification [submitted pursuant to 21 U.S.C. 350b(a)(2) and 21 CFR 190.6]; and (3) prior to the marketing of pyridoxamine dietary supplements, pyridoxamine was authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public.

As discussed more fully below, FDA has concluded that a product containing pyridoxamine is not a dietary supplement under the Act because pyridoxamine is excluded from the dietary supplement definition under the prior market clause in 21 U.S.C. 321(ff)(3)(B)(ii). Accordingly, because products containing pyridoxamine are not dietary supplements, we do not address whether such products are adulterated under 21 U.S.C. 342(f) or other dietary supplement adulteration provisions of the Act.

B. Legal Framework

1. Background

The Dietary Supplement Health and Education Act of 1994 (DSHEA), Pub. L. No. 103-417, 108 Stat. 4325, amended the Act to define the term "dietary supplement" and change the way dietary supplements are regulated. Under section 201(ff)(3)(B) of the Act (21 U.S.C. 321(ff)(3)(B)) (the "prior market clause"), added by DSHEA, the term "dietary supplement" is defined to exclude "an article that is approved as a new drug" or an article "authorized for investigation as a new drug . . . for which substantial clinical investigations have been instituted and for which the existence of such investigations has been public," which was not before such approval or authorization "marketed as a dietary supplement or as a food."

The prior market clause in 21 U.S.C. 321(ff)(3) establishes a system for determining whether articles will be deemed dietary supplements or drugs, and regulated accordingly, depending on how such articles were marketed and categorized when they first entered the marketplace. Stated simply, the prior market clause prohibits the marketing as dietary supplements of

articles that have gained recognition in the marketplace as new drugs by being approved or studied as new drugs.[2] DSHEA reflects Congress's determination that to allow such an article to be marketed as a dietary supplement would not be fair to the pharmaceutical company that brought, or intends to bring, the drug to market, and would serve as a disincentive to the significant investment needed to gain FDA approval of new drugs. The prior market clause does, however, permit continued marketing of a dietary supplement that was first marketed as such or as a food, even if the article is subsequently shown to have therapeutic benefit and is studied or approved as a new drug. In such a case, the dietary supplement was on the market first and should not be penalized simply because a drug manufacturer later chooses to study or seek approval for the article as a new drug.

Under case law interpreting 21 U.S.C. 321(ff)(3)(B), either an entire product or a product component may be "an article that is approved as a new drug" or an article "authorized for investigation as a new drug" for purposes of the prior market clause. *See Pharmanex v. Shalala*, 221 F.3d 1151, 1154-1160 (10th Cir. 2000). *Pharmanex* involved a product called Cholestin that was marketed as a dietary supplement. The sole ingredient in Cholestin was red yeast rice, which is a dietary ingredient under 21 U.S.C. 321(ff)(1). Unlike traditional red yeast rice, however, the red yeast rice in Cholestin had been manufactured to contain high levels of lovastatin, the active ingredient[3] of the prescription drug Mevacor, which is approved to lower cholesterol. In addition to manufacturing Cholestin to contain lovastatin, Pharmanex also marketed Cholestin for its lovastatin content.

After considering these facts, FDA issued an administrative decision finding, *inter alia*, that (1) lovastatin was an "article approved as a new drug" within the meaning of the prior market clause because it was the active ingredient in Mevacor, and (2) by marketing Cholestin as a dietary supplement for its lovastatin content, Pharmanex was also marketing lovastatin, and therefore lovastatin was an "article . . . marketed as a dietary supplement" within the meaning of the prior market clause. Based on these findings, FDA concluded that Cholestin was excluded from the dietary supplement definition because the approval of Mevacor as a new drug preceded Pharmanex's marketing of lovastatin as a dietary supplement.

The district court ruled for Pharmanex, holding that only finished drug products, not individual active ingredients like lovastatin, can be considered "articles approved as new drugs" for purposes of the prior market clause of the dietary supplement definition. The U.S. Court of Appeals for the Tenth Circuit reversed, upholding FDA's interpretation of the term "article" in the prior market clause to include active ingredients as well as finished drug products. The Tenth Circuit, in examining the statutory text, found that "article" in 21 U.S.C. 321(ff)(3) was ambiguous based on, *inter alia*, the contrasting use of the narrower term "product" in other

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[2] There is one exception to this prohibition, but that exception is not relevant here. A product covered by the exclusion in 21 U.S.C. 321(ff)(3)(B)(ii) may be marketed as a dietary supplement if FDA (under authority delegated by the Secretary of Health and Human Services) issues a regulation, after notice and comment, finding that the article would be lawful under the Act. 21 U.S.C. 321(ff)(3)(B).

[3] "Active ingredient" means "any component that is intended to furnish pharmacological activity or other direct effect .... The term includes those components that may undergo chemical change in the manufacture of the drug product in a modified form intended to furnish the specified activity or effect." 21 C.F.R. § 210.3(b)(7). If two molecules are the same active ingredient, they are chemically identical, whereas two molecules that contain the same active moiety may differ chemically, generally by a salt or ester group.

parts of the dietary supplement definition;[4] the use of "article" in the drug definition to refer to both finished drug products and their components,[5] and on provisions of the Act and FDA regulations indicating that active ingredients, as well as finished drug products, are the subject of clinical investigations and are approved in the new drug application process.[6] *Pharmanex*, 221 F.3d at 1155-56. After concluding that the meaning of "article" in the prior market clause was ambiguous, the court of appeals held that FDA's interpretation of that term to include active ingredients was entitled to deference under *Chevron, U.S.A. v. Natural Resources Defense Council*, 567 U.S. 837, 104 S. Ct. 2278, 81 L.Ed.2d 694. The court found that FDA's interpretation "comport[ed] with common sense and the overall purposes of the [Act]" in that under a contrary interpretation limiting "article" to finished products, manufacturers would be able to market dietary supplements with components identical to the active ingredients in approved drugs. *Id.* at 1159-60. To adopt such an interpretation, the court concluded, would render the exclusion from the dietary supplement definition in 21 U.S.C. 321(ff)(3)(B) meaningless and contravene the fundamental purposes of the Act by allowing manufacturers to evade the safety and efficacy requirements for new drugs and undermining incentives for drug development. *Id.* at 1159.

2. Active Moiety Issue

Under the holding of *Pharmanex* that "article" includes active ingredients, it is clear that pyridoxamine dihydrochloride, the active ingredient of Pyridorin, is an "article authorized for investigation as a new drug" within the meaning of the prior market clause. But because your petition requests that FDA determine the regulatory status of *all* pyridoxamine products marketed as dietary supplements, not only those that contain the dihydrochloride salt of pyridoxamine, it is necessary for us to consider whether pyridoxamine, the active moiety[7] of pyridoxamine hydrochloride, is also an "article authorized for investigation as a new drug."

In the November 18, 2005, Federal Register notice requesting comment on the status of pyridoxamine, FDA tentatively concluded that "pyridoxamine, the active moiety of pyridoxamine dihydrochloride, is excluded from the dietary supplement definition under the exclusion clause in 21 U.S.C. 321(ff)(3)(B)(ii)." 70 Fed. Reg. at 69,976 (footnote omitted). Although the agency received several comments asserting that the exclusion did not apply because pyridoxamine was marketed as a food or dietary supplement before the IND for pyridoxamine dihydrochloride went into effect, FDA received no comments on the threshold issue of whether an active moiety of a drug under IND is an "article authorized for investigation as a new drug" under the prior market clause.

Pharmanex did not present the active moiety issue because in that case, the active ingredient and active moiety of the "article . . . approved as a new drug" were the same, lovastatin. Here, however, the active ingredient and the active moiety differ. Although pyridoxamine dihydrochloride is the substance described in the IND for Pyridorin, the substance that is

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[4] *See* 21 U.S.C. 321(ff)(1), (ff)(2).
[5] *See* 21 U.S.C. 321(g) (definition of "drug").
[6] *See, e.g.*, 21 U.S.C. 355(c)(3)(E); 21 CFR 312.23(a)(7)(i).
[7] "Active moiety" is defined in 21 CFR 314.108(a) and 316.3(b)(2). *See supra* note 1.

actually being studied for its physiological or pharmacological action is pyridoxamine, the active moiety of pyridoxamine dihydrochloride.

The underlying principle of the prior market clause is that substances that have been studied for a drug indication or have gained recognition in the marketplace as new drugs may not be incorporated into, or marketed as, dietary supplements. A dietary supplement with the same active moiety as an approved new drug poses the same concerns as a dietary supplement that contains the active ingredient of an approved new drug. Pyridoxamine would be expected to have the same general physiological and pharmacological effects as pyridoxamine dihydrochloride, since compounds with the same active moieties generally have the same effects in the body. Although the salt or ester group may affect the bioavailability of the active moiety, in almost all cases it does not affect the pharmacological activity of the compound (Ref. 1). Thus, the marketing of pyridoxamine in a dietary supplement is essentially equivalent to the marketing of an investigational new drug as a dietary supplement.

The holding of *Pharmanex* that a product component may be an "article . . . approved as a new drug" or an "article authorized for investigation as a new drug" within the meaning of the prior market clause ensures that substances that have been approved or studied as new drugs may not be sold as dietary supplements. Although *Pharmanex* was decided in the context of active ingredients, the court's rationale for upholding FDA's interpretation of "article" as including a component of a drug also applies to active moieties. As discussed below, FDA's interpretation of the Act and its regulations in several other contexts supports the conclusion that the active moiety is the essential characterizing component of a drug and that the salt or ester group of the active ingredient, while significant, is less important.

- Orphan Drugs

Sections 525-528 of the Act (21 U.S.C. 360aa-360dd) provide incentives for the development of drugs for rare diseases and conditions, known as orphan drugs.[8] Section 527(a) states:

> [I]f the Secretary ... approves an application filed pursuant to section 505 [21 U.S.C. 355] ... for a drug designated ... for a rare disease or condition, the Secretary may not approve another application under section 505 ... for such drug for such disease or condition for a person who is not the holder of such approved application ... until the expiration of seven years from the date of the approval of the approved application.

FDA's interpretation of the phrase "such drug" in this provision is based on the concept that two drugs with the same active moiety can generally be expected to be the same in the most relevant respect, their pharmacological activity. Under the agency's orphan drug exclusivity regulations, seven years of marketing exclusivity are granted to the first orphan drug to be approved for use in a given orphan disease or condition. For drugs composed of small

[8] Orphan drug designation is granted if a drug is being or will be investigated for a "rare disease or condition," defined as a disease or condition that affects less than 200,000 people in the United States, or a disease or condition that affects more than 200,000 people in the U.S. if there is no reasonable expectation that the cost of developing and making the drug in the U.S. will be recovered from U.S. sales of the drug. 21 U.S.C. 360bb(a).

molecules,[9] this exclusivity is a protection against approval of another drug for the same orphan use that has the same active moiety, whether or not it has the same active ingredient as the protected drug. Until the seven-year period of exclusivity for the first drug expires, approval will not be granted for any other drug that is intended for the same orphan indication that contains the same active moiety unless the drug with the same active moiety is shown to be clinically superior to the first drug. 21 CFR 316.3(b)(13), 316.31. In the preamble to the proposed orphan drug rule, FDA explained that its use of the active moiety principle to distinguish between drugs was based on the fact that drugs that differ in the chemical structure of their active moieties are highly likely to have pharmacologic differences. Orphan Drug Regulations, Proposed Rule, 56 Fed. Reg. 3338, 3341 (Jan. 29, 1991).

FDA's regulatory interpretation of "such drug" in the orphan drug provisions of the Act as meaning a drug with the same active moiety was upheld in *Baker Norton Pharmaceuticals v. FDA*, 132 F. Supp. 2d 30 (D.D.C. 2001). The court followed the reasoning in *Pharmanex* in finding that the term "drug" could have different meanings throughout the statute, was ambiguous, and that the agency's interpretation was permissible.

- Pediatric Marketing Exclusivity

Section 505A of the Act (21 U.S.C. 355a) extends the marketing exclusivity for new drugs for six months if, at FDA's request, the manufacturer studies the use of the drug in children and submits reports of the studies to FDA in a new drug application (NDA) or NDA supplement that proposes pediatric labeling based on the results of the studies.

In *National Pharmaceutical Alliance v. Henney*, FDA was challenged on its interpretation of "drug" in 21 U.S.C. 355a to mean active moiety. 47 F. Supp. 2d 37 (D.D.C. 1999). The effect of this interpretation, which was presented in guidance, was to allow a manufacturer who submits the requested studies on use of an active moiety in children to receive pediatric marketing exclusivity[10] for its entire line of drug products containing that active moiety, not just the specific drug product(s) studied. The court held under *Chevron* that the statute was ambiguous and that FDA's interpretation was permissible. 47 F. Supp. 2d at 39-40.

- Hatch-Waxman Marketing Exclusivity for New Drugs

The Act's Hatch-Waxman exclusivity provisions for new drugs provide for different periods of exclusivity depending on whether the active ingredient of the drug has been previously approved. Under 21 U.S.C. 355(j)(5)(F)(ii), when FDA approves an application for a new drug, "no active ingredient (including any salt or ester of the active ingredient) of which has been approved" in another NDA, the drug receives five years of marketing exclusivity. On the other hand, when FDA approves an application for a new drug that includes "an active ingredient (including any salt or ester of the active ingredient)" that has been previously

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[9] Pyridoxamine dihydrochloride is a small molecule for purposes of 21 C.F.R. 316.3(b)(13) in that it consists of a single active moiety that is not a macromolecule. A macromolecule is a large molecule such as a polymer or protein that is made up of many smaller structural units (Ref. 2).

[10] I.e., a six-month extension of the exclusivity period to which the product would otherwise be entitled.

approved in another NDA, the drug may receive only three years of marketing exclusivity. 21 U.S.C. 355(j)(5)(F)(iii).

FDA interprets "active ingredient" in the phrase "active ingredient (including any salt or ester of the active ingredient)" to mean active moiety.[11] Consistent with the exclusivity provisions in the statute, the agency's regulations provide that five-year exclusivity will be granted for drug products that contain "new chemical entities," defined as drugs that contain no active moiety that has previously been approved under 21 U.S.C. 355. 21 C.F.R. 314.108(a), (b)(2). Three-year exclusivity may be granted for drug products that contain an active moiety that has previously been approved. 21 C.F.R. 314.108(b)(4)(iii).

The Hatch-Waxman exclusivity provisions reflect that drugs with different active moieties than those already approved deserve greater exclusivity than drugs with the same active moieties, but also recognize the potential value of different products that contain the same active moiety but have different active ingredients or differ in other ways (e.g., dosage, route of administration, indication). The longest exclusivity offered (currently five years) is granted only for drugs that have a different active moiety than any other approved drug, consistent with the notion that drugs with different active moieties can be expected to have different pharmacologic properties and to require a greater quantum of data and information to support approval, and that such drugs therefore deserve a longer period of exclusivity.

In summary, FDA's interpretation of "article" in the prior market clause to include active moieties is consistent with other provisions of the Act governing drug marketing exclusivity. In the orphan drug context, the seven-year marketing exclusivity granted to the first drug approved for an orphan disease or condition protects the active moiety of the drug, meaning that no drug with the same active moiety may be approved for the same disease or condition until the first drug's exclusivity expires. In the pediatric context, a drug manufacturer may receive six months of additional marketing exclusivity for all of its drug products with the same active moiety by conducting a pediatric study of a single drug with that active moiety. In the Hatch-Waxman exclusivity context, the longest period of exclusivity is given to drugs that have an active moiety never before approved in the United States, recognizing that drugs with a new active moiety can be expected to have different pharmacologic properties than other approved drugs already on the market, and therefore represent a more significant advance in pharmaceutical science and a greater contribution to the armamentarium of therapeutic tools available to doctors.

Approval of active ingredients and active moieties is integral to the new drug approval process. While it is true that a new drug approval under 21 U.S.C. 355 is for a finished drug product, it is also true that the approval of a particular new drug includes within its scope all of the necessary elements of a new drug application, including the drug's active moiety and its active and inactive ingredients. *See* 21 U.S.C. 355(b)(1); 21 CFR 314.50; *Pharmanex*, 221 F.3d at 1156. This does not mean that an NDA can be filed for an active ingredient or active moiety in isolation or that a particular active ingredient or active moiety that has been approved as a component of a new drug is approved for marketing as a separate entity. Rather, active

[11] Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, Final Rule, 59 FR 50,338, 50,358 (Oct. 3, 1994).

ingredients and active moieties are approved in combination with other ingredients for particular conditions of use, as specified in the approved application. In the case of active moieties, the active moiety is also approved for use in a particular form (e.g., salt or ester). Multiple provisions of the Act contemplate that active ingredients and active moieties are approved as new drugs under section 355. *See* 21 U.S.C. 355(c)(3)(E)(ii)-(iii) (providing varying periods of market exclusivity for drugs, depending on whether they contain "an active ingredient (including any ester or salt of the active ingredient)"[12] that has been previously approved); 379g(1) (defining "human drug application" for user fee purposes to include new drug applications submitted under 21 U.S.C. 355(b)(2) that "request[] approval of a molecular entity which is an active ingredient (including any salt or ester of an active ingredient)" that has not been previously approved). *Cf.* 21 U.S.C. 360b(d)(4) (referring to new animal drugs containing more than one active ingredient where "the active ingredients . . . have previously been separately approved for particular uses and conditions of use . . . .").

FDA's interpretation of "article" in the prior market clause to include active moieties is consistent with the holding of *Pharmanex* and with the purposes of the prior market clause. To interpret the meaning of the term "article" in this provision otherwise would enable a dietary supplement manufacturer to evade the prohibition against the use of approved or investigational new drugs in a dietary supplement by formulating a product containing a different ester, salt, or other noncovalent derivative of the active moiety. To allow the marketing of such a product as a dietary supplement would serve as a disincentive to new drug development because drug manufacturers would not be willing to bring new products to market knowing that products containing different forms of the active moiety as active ingredients could be marketed as dietary supplements without having to go through the new drug approval process.

Similarly, interpreting "article" in the prior market clause to exclude active moieties would undermine the generic drug approval system. A generic drug may be marketed only after a manufacturer has filed an abbreviated new drug application (ANDA) and received approval under 21 U.S.C. 355(j). If the term "article" referred solely to finished drug products and their active ingredients, a company could formulate a product with the same active moiety as an approved new drug, append a salt or ester group, and thereby create a new product that could be marketed as a dietary supplement. To allow such marketing would serve as a disincentive to new drug development because drug manufacturers would not be as willing to make the substantial investment necessary to research, develop, and bring to market "pioneer" new drugs if products containing the active moieties of these drugs as components could be marketed as dietary supplements without having to go through the ANDA process. Nor would generic drug companies likely be willing to submit ANDAs for products that could more easily be marketed as dietary supplements by simply varying the salt or ester group bonded to the active ingredient. Thus, FDA's interpretation of "article" in the prior market clause to include active moieties is consistent with the Congressional purpose that DSHEA not undermine incentives for the development and approval of new drugs, whether pioneer or generic.

C. Status of Pyridoxamine under 21 U.S.C. 321(ff)

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[12] As explained above in the discussion of Hatch-Waxman exclusivity, FDA interprets "active ingredient" in this context to refer to the active moiety of the drug's active ingredient.

1. Pyridoxamine is an article authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public

The IND for pyridoxamine dihydrochloride was sent to FDA in July 1999, received on August 2, 1999, and went into effect on September 1, 1999 (Ref. 1). Thus, pyridoxamine was authorized for investigation as a new drug under an IND on September 1, 1999.[13]

To determine whether substantial clinical investigations of pyridoxamine have been instituted and made public, FDA reviewed the relevant evidence in the administrative record of this proceeding. Information provided in your petition demonstrates that the existence of three studies of pyridoxamine has been made public. In a press release issued on September 8, 1999, BioStratum announced that it had initiated human clinical studies of Pyridorin (Ref. 3). BioStratum presented the results from three Phase II clinical investigations of Pyridorin at the American Diabetes Association meetings in June 2004. BioStratum announced the existence of those studies and their results in a press release on June 7, 2004 (Ref. 4). One study described in the press release was a six-month double-blind Phase IIa trial involving 128 patients with type 1 or type 2 diabetes and diabetic nephropathy. The other two were six-month multi-site, double-blind Phase IIb trials involving a total of 84 patients with type 1 or type 2 diabetes and either mild-to-moderate or moderate-to severe diabetic nephropathy. All three trials were randomized and placebo-controlled. .

The Act does not define "substantial clinical investigations" or specify the criteria that should be considered in deciding whether clinical investigations of a drug are "substantial" under 21 U.S.C. § 321(ff)(3)(B)(ii). Under any reasonable definition of the term, however, FDA concludes that the human studies of Pyridorin described in your petition fall well above the minimum threshold to qualify as "substantial clinical investigations." Moreover, the existence of these substantial clinical investigations has been made public, as demonstrated by the press releases submitted in support of your petition.

2. Pyridoxamine was not marketed as a dietary supplement or as a food before it was authorized for investigation as a new drug.

The fact that pyridoxamine is authorized for investigation as a new drug does not automatically exclude it from being a dietary supplement. This is because under the prior market clause in 21 U.S.C. 321(ff)(3)(B)(ii), pyridoxamine would still qualify as a dietary supplement if it had been "marketed as a dietary supplement or as a food" before being authorized for investigation as a new drug on September 1, 1999.

[13] Under FDA's IND regulations, an IND goes into effect thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are on clinical hold. Once the IND is in effect, the article that is the subject of the IND is authorized for use in a clinical investigation, provided that the sponsor complies with all applicable requirements with respect to the conduct of the clinical investigation. The IND may go into effect earlier than 30 days after FDA receives it if FDA so notifies the sponsor. *See* 21 CFR 312.40.

The most obvious way to show that an article has been "marketed as a dietary supplement or as a food" is with evidence that the article itself has been sold or offered for sale in the U.S. as a dietary supplement or as a food. For example, a catalog listing a product identified as a "pyridoxamine supplement" would establish the marketing of pyridoxamine as a dietary supplement. Similarly, business records documenting that pyridoxamine was offered for sale or sold as an ingredient for use in manufacturing baked goods or other conventional foods would establish the marketing of the substance as a food.

It is not necessary to show that an article has been marketed as a food or dietary supplement in isolation to establish prior marketing, however. A component of a product may, under certain circumstances, constitute an "article . . . marketed as a dietary supplement or as a food." The relevant inquiry in determining whether a component present in a marketed product qualifies as such an article for purposes of the prior market clause is whether, in marketing the product, a firm was also marketing the component itself as a food or as a dietary supplement by, e.g., making claims about the component or otherwise highlighting its presence in the product. *See Pharmanex v. Shalala*, 2001 WL 741419, at *4 & n.5 (D. Utah March 30, 2001). For example, in *Pharmanex*, the firm marketed lovastatin, a component of its red yeast rice product Cholestin, by promoting the lovastatin content of Cholestin. *Id.* at *3.

The comments submitted to this proceeding in response to the November 18, 2005 Federal Register notice do not establish that pyridoxamine was marketed as a food or a dietary supplement before the IND went into effect. Two comments stated that pyridoxamine is present in various common foods, such as frozen fish, fresh and dried yeast, milk, eggs, beef, chicken, and pork. One of these comments stated, "[F]or decades U.S. consumers have regularly bought and consumed Brewer's Yeast for its Vitamin B6 content and benefits." However, neither of these comments provides any evidence that any of the foods mentioned were promoted specifically as pyridoxamine sources or otherwise marketed for their pyridoxamine content. Moreover, neither comment contains any documentation that these foods were marketed with reference to any property that they might have as a consequence of their pyridoxamine content. Thus, even if these foods contain high levels of pyridoxamine, that fact alone does not constitute evidence that pyridoxamine was marketed as a food or a dietary supplement within the meaning of DSHEA's prior market clause.

The mere presence of a substance authorized for investigation as a new drug as a component of a product found in the food supply does not by itself establish that the substance was "marketed" within the meaning of 21 U.S.C. 321(ff)(3)(B)(ii). Rather, as discussed above, circumstances must establish that in marketing a product containing such a component, a firm was also marketing the component. The plain language of section 321(ff)(3)(B)(ii) preserves dietary supplement status only for those articles approved or authorized for investigation as new drugs that were "before such approval . . . or authorization *marketed as* a dietary supplement or as a food" (emphasis added). Judging by Congress's choice of language, Congress did not intend to preserve dietary supplement status for articles that were merely present in the food supply before being approved or authorized for investigation as new drugs. The prior market clause requires the article to be marketed "as", not merely "in," a food or dietary supplement. Moreover, Congress used the phrase "present in the food supply" elsewhere in DSHEA, but chose not to use the phrase in the prior market clause. *Compare* 21

U.S.C. 350b(a)(1) *with* 21 U.S.C. 321(ff)(3). To argue that the mere presence of a substance in the diet preserves dietary supplement status would mean that even a few molecules of a substance never before recognized as therapeutically beneficial would, if present in some food, defeat any incentives for pharmaceutical manufacturers to develop such a substance into a new drug.

The record before the agency contains no convincing evidence that pyridoxamine was marketed as a dietary supplement or food before it was authorized for investigation as a new drug. In addition to the previously discussed comments pointing to the presence of pyridoxamine in various long-marketed conventional foods, FDA received two comments concerning the marketing of pyridoxamine as a dietary supplement. One comment from a trade association asserted that pyridoxamine was marketed as a dietary supplement before October 15, 1994. The comment stated that "we have interviewed retired industry executives and academics and other people who were close to the industry prior to that time, and several recall that pyridoxamine was marketed in dietary supplements prior to October 15, 1994." The comment did not, however, name the individuals who recall the marketing of pyridoxamine or give any other specifics (e.g., product name, company name). The comment added that pyridoxamine's marketing before its authorization for investigation as a new drug is further evidenced by its inclusion in dietary supplement industry lists of "grandfathered" ingredients, i.e., dietary ingredients marketed before October 15, 1994. *See* 21 U.S.C. 350(c). This comment contained an affidavit from a former officer of the trade association describing how the association's list was compiled. Another comment from a dietary supplement manufacturer contained an affidavit from a former industry executive stating the executive's recollection that at least one dietary supplement containing pyridoxamine had been marketed before the substance was authorized for investigation under an IND. However, neither of these comments offered any documentation, such as a catalog or product labeling from the relevant time period, to support the affidavits' assertions that dietary supplements containing pyridoxamine were marketed before pyridoxamine's authorization under an IND.

Although FDA has no reason to doubt that a person who submits an affidavit attesting to his or her recollection of when a dietary ingredient was first marketed is honestly stating his or her present beliefs, we do not believe that such assertions alone, without any sort of objective, verifiable documentation from the time of marketing, are an adequate basis to establish prior marketing of a substance as a dietary supplement or as a food. Memory is subjective and can be unreliable. This is particularly true when an affidavit relates to events that occurred a decade or more before it was executed, as is the case with both affidavits submitted in this proceeding. To accept affidavits based solely on memory, with no supporting documentation, would set an evidentiary burden so low as to undermine the purpose of the prior market clause.

Similarly, the fact that pyridoxamine appears on an industry-generated list of allegedly grandfathered dietary ingredients does not constitute evidence sufficient to establish that pyridoxamine was marketed as a dietary supplement before it was authorized for investigation as a new drug. The affidavit submitted with the trade association comment described above states that the substances on the industry grandfathered ingredient list were placed on the list because they were ingredients of products for which labels were submitted to a second trade association by member companies as part of a label verification program. According to the

affidavit from the official of the first trade association, the second trade association maintained contemporaneous records of information submitted to the label verification program, and these records were used to generate a list of dietary supplement products and ingredients marketed before October 15, 1994. However, an affidavit submitted by an official of one trade association is not necessarily reliable as to the activities and records of another trade association. Moreover, neither trade association submitted any marketing data on pyridoxamine from the label verification program records that the affidavit identified as the source of the list of grandfathered ingredients. Therefore, FDA was unable to determine the nature and age of the records kept as part of the label verification program or to evaluate whether such records do, in fact, demonstrate the marketing of pyridoxamine before October 15, 1994.

Further, both the affidavit and the trade association's introduction to the list state that the association did not independently verify when the substances in the list were first marketed, and the cover page of the list specifically states, "This list . . . does not constitute verification that any specific dietary ingredient was or was not marketed as a dietary supplement before October 15, 1994." Moreover, the trade association's introduction to the list states, "There is no definitive list of 'grandfathered' dietary ingredients. . . . The best policy is for any company to maintain its own records confirming longterm use of an ingredient." Accordingly, the presence of a substance on this industry list of "grandfathered" dietary ingredients does not constitute an adequate basis to conclude that the substance is not subject to the exclusion clause in the absence of independent, verifiable evidence that the substance was marketed as a food or a dietary supplement prior to its authorization for investigation as a new drug under an IND.

3. Other Issues Raised in Comments

Several comments received in response to the November 18, 2005 Federal Register notice argued that pyridoxamine is a dietary ingredient because it is a naturally occurring form of vitamin B6. One comment stated that "Pyridoxamine is unequivocally a dietary ingredient because it is one of the three primary natural forms of vitamin B6, and it is one of the two predominant forms in animal products used as human foods." Another comment stated that "Vitamin B6 is [sic] water-soluble vitamin that exists in three major chemical forms: pyridoxine, pyridoxal, and pyridoxamine..." These comments confuse the prior market clause in 21 U.S.C. 321(ff)(3)(B) with the requirement in 21 U.S.C. 321(ff)(1) that a dietary supplement bear or contain one or more dietary ingredients. FDA agrees that pyridoxamine is a dietary ingredient, but that is not relevant with respect to whether pyridoxamine is excluded from the dietary supplement definition under the prior market clause in section 321(ff)(3)(B). Because the elements of the dietary supplement definition in section 321(ff)(1), (2), and (3) are phrased conjunctively (separated by "and"), a product qualifies as a dietary supplement only if it satisfies the criteria in all three of these paragraphs. Demonstrating that a product satisfies the requirement in section 321(ff)(1) to contain a dietary ingredient does not establish that the product meets the other criteria in section 321(ff)(2) and (ff)(3), and there are many products that contain a dietary ingredient but nonetheless are not dietary supplements (e.g., topical vitamin products, which are not "intended for ingestion" as required by section 321(ff)(2)).

D. Adulteration and Misbranding Issues

Your petition expresses concern that firms marketing pyridoxamine products as dietary supplements are making illegal disease claims that lack adequate substantiation. The petition cites examples of such claims from an Internet site and asserts that claims of this nature cause the pyridoxamine products to be misbranded under the Act and to pose a safety risk to consumers, who may rely on these products to treat serious diseases (e.g., arteriosclerosis and diabetic retinopathy). The petition further states that analysis of samples from one pyridoxamine dietary supplement product revealed the presence of high levels of an impurity with toxic potential. Based on this finding and on data from ConsumerLab.com concerning levels of impurities found in other dietary supplements, the petition contends that pyridoxamine dietary supplement products pose a health risk to the public because they are not manufactured in accordance with current good manufacturing practice.

As explained earlier, FDA has concluded that products containing pyridoxamine are not dietary supplements. Consequently, we are not addressing your allegations regarding adulteration and misbranding of these products under the dietary supplement provisions of the Act.

We share your concern about products that may pose a health risk to consumers and thank you for the analytical and other information provided in the petition. We encourage you to continue to report problems with FDA-regulated products to us so that we can evaluate the situation and take any necessary action.

III. Conclusion

Pyridoxamine dihydrochloride is authorized for investigation as a new drug under the name Pyridorin. The IND for pyridoxamine dihydrochloride was filed with FDA in July 1999 and went into effect on August 2, 1999. Substantial clinical investigations have been conducted and the existence of those studies has been made public. There is no verifiable, contemporaneous evidence documenting that pyridoxamine dihydrochloride or any other compound containing pyridoxamine as its active moiety was marketed as a dietary supplement or as a food prior to pyridoxamine's authorization for investigation as a new drug under an IND. Accordingly, a product containing pyridoxamine is not a dietary supplement as defined in 21 U.S.C. 321(ff) and may not be marketed as such. For the reasons stated above, FDA has granted your request to establish a new docket for your citizen petition and denied your requests that the agency 1) state in writing that dietary supplements that contain pyridoxamine are adulterated under the Act and 2) exercise its enforcement authority under the Act to remove from United States interstate commerce dietary supplements containing pyridoxamine.

Sincerely,

Michael A. Chappell
Acting Associate Commissioner
for Regulatory Affairs